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A STUDY OF LIVER DISEASE IN BILHARZIAL SUBJECTS INFECTED WITH V--ETC(U)
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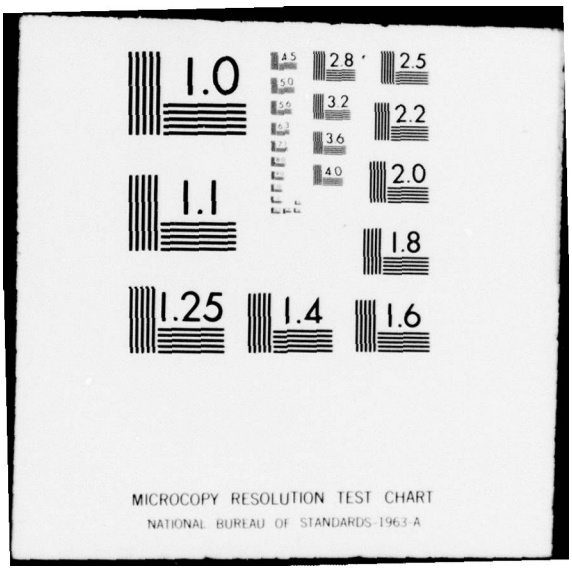
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A STUDY OF LIVER DISEASE IN BILHARZIAL SUBJECTS INFECTED WITH VIRAL HEPATITIS IN UPPER EGYPT.

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The main objective of the study is to study the course of liver disease in patients suffering from schistomiasis after being infected with viral hepatitis.

For the specific objectives and approach please consult the original protocol.

Material and Methods :

The subjects of this study were selected from patients admitted to Assiut Fever Hospital with a clinical diagnosis of viral hepatitis starting from July 1973. The only criterion for selection was the suitability of the patient for a long period of follow up. This entails consideration of the remoteness of the patient's village from Assiut, his readiness to cooperate, liability to leave the area etc...

All patients were subjected to the following studies.

1. A base-line clinical examination in which the history of exposure, symptoms and therapy of schistomiosis are obtained. Also history of contact with jaundiced patients, injections, operations or exposure to hepatotoxic agents is obtained. A full clinical examination according to a specially designed sheet is carried out.

2. An every other day recording of clinical progress till discharge from hospital.

3. On admission into the trial, and weekly thereafter till discharge, the following tests are performed.

- Routine urine examination including looking for schistosome eggs .
- Parasitological examination of stools.
- Examination of rectal snips for schisto. ova (once).
- Liver biopsy (once). A part is examined fresh for schisto ova and a part is examined histologically.
- Liver function rests: serum bilirubin, SGOT, SGPT, alkaline phosphatase and serum proteins.
- Full haematological study.
- HB_s Ag (Hepatitis B surface antigen) by counterelectrophoresis.
- Virological testing of urine, stools and serum using standard techniques in the central virological Labs at Agouzah.

4- Follow up :

On discharge. The patient recieves a card on which dates of follow up are stated. Letters are sent to every patients to remind him of each date. A messenger is sent to those who fail to show in the expected dates and all patients who attend for follow up recieve free medicines and money as

incentives. At each follow up , all the baseline clinical and laboratory investigations are repeated except liver and rectal biopsies. Only recently we started to perform a second liver biopsy for patients followed up for at least 9 months.

Dates of follow up : Every 3 months for one year, then every 6 months of 5 years (or for the time of the study).

Results

So far 230 patients have been admitted to the study. This report covers 208 patients whose data were ready for analysis at the time of preparation.*

Sex and age distribution : see tables 1a and 1.b

Sex	Number	Age Range Yrs.	Age Mean Yrs.
Males	141	4-66	24.2
Females	67	2-50	20.1
Total	208	2-66	21.6

Table 1.a : Age and sex distribution of 208 patients with viral hepatitis.

* Haematological and detailed histopathological data are not analysed in this report.

** Statistical analysis not included in this report as new data are continually entered.

Age group (Yrs.):		0-5	>5-10	>10-15	>15-10	>20-30	>30-40	>40-50	>50-60	>60-70
Males (141)	Number	7	26	26	31	16	15	12	6	2
	%	5.0	18.4	18.4	22.0	11.3	10.6	8.5	4.3	1.4
Females (67)	Number	4	11	13	14	18	5	2	0	0
	%	6.0	16.4	19.4	20.9	26.9	7.5	2.9		
Total (208)	Number	11	37	39	45	34	20	14	6	2
	%	5.3	17.8	18.8	21.6	16.3	9.6	6.7	2.9	0.96

Table 1.b : Age distribution of 208 patients with viral hepatitis (age groups).

Hepatitis B. Antigen (HB_s Ag)

Results of serum testing by counterelectrophoresis (Table 2).

	HB_s Ag positive		HB_s Ag negative	
	Number	(%)	Number	(%)
Males (141)	68	(48.2)	73	(51.8)
Females (67)	35	(52.2)	32	(47.8)
Total (208)	103	(49.5)	105	(50.5)

Table 2 : Incidence of HB_s Ag in 208 patients with viral hepatitis.

Evidence of Schistosomiasis :

A patient is considered to be suffering from schistosomiasis if one or more of the following conditions is evident.

1- Living and/or dead S. haematobium ova in urine (24 hour urine sediment on 3 consequetive days).

2- Living or dead ova in stools.

3- Ova in rectal snips.

4- Ova in freshly examined liver biopsy.

5- Unequivocal evidence of schistomal hepatic involement in histopathological examination of liver biopsy.

According to these criteria the patients could be divided into two groups, schistosomal and non-schistosomal. (Table 3).

Occurrence of HB_s Ag among Schistosomal and Non-Schistosomal patients. (See Tables 4.a and 4.b).

These is no significant difference between the occurrence of HB_s Ag in the schisto and Non-schisto groups.

Liver Biopsy :

Liver biopsy has been performed in 175 out of the 208 patients. Most of the missing cases were among the early admitted cases when children and some females were not biopsied. Since many months proctically all patients are being biopsied.

Fresh liver biopsy examination for schisto ova, by compressing the tissue between two slides and examining by the low power of the microscope proved of little or no value as such a finding was rare and in not a single case were ova found this way in which histopathological evidence was lacking.

Group	Sex & Number	Age range (Yrs.)	Age Mean (Yrs)	0-5	> 5-10	>10-15	>15-20	>20-30	>30-40	>40-50	>50-60	>60-70
Non-Schisto 116 patients	Males (57)	5-66	25.7	5 (8.7)	12 (21)	5 (8.7)	7 (12.3)	5 (8.7)	9 (15.8)	8 (14)	4 (7)	2 (3.5)
	Females (59)	2-50	20.5	4 (6.8)	10 (16.9)	10 (16.9)	12 (20.3)	16 (2731)	5 (8.5)	2 (3.4)	0	0
	M+F 116	2-60	23.1	9 (7.5)	22 (18.9)	15 (12.9)	19 (16.4)	21 (18.1)	14 (12)	10 (8.6)	4 (3.4)	2 (1.7)
Schisto-somal 92 pat-ients	Males (84)	4-60	19.9	2 (2?4)	14 (16.7)	21 (25)	24 (28.6)	11 (13.1)	6 (7.1)	4 (4.8)	2 (2.4)	0
	Females (8)	9-25	17.3	0	1 (12.5)	3 (37.5)	2 (25)	2 (25)	0	0	0	0
	M+F (92)	4-60	19.7	2 (2?2)	15 (16.3)	24 (26.1)	26 (28.3)	13 (14.1)	6 (6.5)	4 (4.3)	2 (2.2)	0 0

Table 3 : Sex and age analysis of the schistosomal and non-schistosomal groups.

* Age groups in years. Percentages are between brakets.

Non-Schisto patients	HB_s Ag +		HB_s Ag -	
	No.	%	No.	%
Males (57)	26	(45.6)	31	(55.4)
Females (59)	32	(54.2)	27	(45.8)
Total (116)	58	(50.0)	58	(50.0)

Table (4.a): Occurrence of HB_s Ag.. among Non-schistosomal patients.

Schistosomal patients	HB_s Ag +		HB_s Ag-	
	No.	%	No.	%
Males (84)	42	(50)	42	(50)
Females (8)	3	(37?5)	5	(62.5)
Total (92)	45	(48.9)	47	(51.1)

Table (4.b): Occurrence of HB_s Ag among schistosomal patients.

- Detailed histopathological examination is performed using : Haematoxylin and Eosin, P.A.S., Perl's stain, Reticulin stain & Trichrome stain. The detailed analysis of liver biopsy studies will be reported on subsequently.

Rebiopsy : 3 patients have been rebiopsed 9-12 months after onset of their illness. This is a new trial which will be persued whenever acceptable to the patient.

Liver function tests :

A detailed analysis will be reported upon subsequently

Virological Studies :

The following viruses have been isolated :

1- Viruses isolated from stools (200 patients):

Enteroviruses :		
Coxsaki A	3	25
Coxsaki B	9	
ECHO	8	
Polio	5	
Cytomegalic V.		5
Adenoviruses		11
Unidentified viruses		14
Negative		145

2- Viruses isolated from urine samples (172)

Cytomegalic viruses	9
Unidentified	2
Negative	161

Dr. June Almeida of the wellcome Research Laboratories, kent, England has kindly accepted to help in identifying the unidentified viruses and the samples have been sent to her and the result is awaited for. We are now in the process of evaluating the significance of the viruses isolated. Detailed correlation with the clinical features, histopathological and laboratory findings in every case is being performed.

Isolates from serum samples are being verified and identified

Follow-up and Outcome :

Out of the 208 cases analysed, the success of follow up April 1st. 1975 is as follows :

25	patients	5th. follow-up	(1½ years)
20	"	4th. " "	(1 years)
27	"	3rd. " "	(9 months)
37	"	2nd. " "	(6 ")
31	"	1st. " "	(3 ")
140			

63 patients did not appear at follow up till that date,

of whom 20 appeared after that and are not analysed in this report. There is little hope that the remaining 43 will be available for follow up.

Severe Complications :

7 patients developed fulminant hepatitis (3.36 %). 6 passed into grade IV coma of whom one survived and 5 died (2.4 % fatality rate).

One patient passed into grade II coma and survived. In table (5) the 5 total cases are described.

Case No.	Sex	Age	Schisto	HB_s Ag	Remarks
92	Male	18	+	+	Living schisto ova in urine
161	"	9	+	+	" " " " " , hookworm in stools, coxc. B. virus in stools.
109	Female	30	-	-	Pregnant 6 month. Coms. A v. in stools .
133	"	25	-	+	Lactating.
206	"	30	-	+	Delivered a dead infant one month before admission, adenovirus in stools.

Table (5): Relevant data of 5 total cases of viral hepatitis.

Chronic sequelae :

For the sake of this report which is prepared when only 45 patients are followed-up for more than one year, chronicity will mean the presence of one or more of the following criteria for more than 180 days following the onset of the illness :

- Transaminasaemia.
- Bilirubinaemia.
- HB_s antigenaemia.
- A firm hepatomegaly 2 fingers at least below the right costal margin ± splenomegaly.

Thus, from the total 208 patients, the outcome of 145 patients is considered to be known within the above limtations. This would includ the 5 deaths. Following is the analysis of the 145 patients :

Outcome :

Recovery	81 (55.9 %).
Chronicity	59 (40.7 %).
Death	5 (3.4 %).*
	145

* Deaths 2.4 % of the toral 208 cases.

Relation ship to sex :

	Males	Females
Recovery	48 (48 %)	33 (73.3 %)
Chronicity	50 (50 %)	9 (20 %)
Death	2 (2 %)	2 (6.7 %) **
	100	45

** Death 1.4 % from 141 males and 4.47 from 67 females.

Relationship to HB_s Ag :

	HB_s Ag +	HB_s Ag -
Recovery	36 (49.3 %)	45 (62.5 %)
Chronicity	33 (45.2 %)	26 (36.1 %)
Death	4 (5.5 %)	1 (1.4 %) *
	73	72

* Deaths 3.9 % from 103 Ag+ and 0.95 % from 105 Ag- patients.

The outcome and chronic sequelae among the Non-schistosomal and schistosomal groups.

Out of the 145 patients analysed above, 80 fell in the Non-schistosomal group (35 males and 42 females) and 65 in the schistosomal group (62 males an 3 females). The outcome and sequelae of the 2 groups of patients are considered in table 6 in which the two groups are considered as a whole, according to the sex distribution and to the occurrence of HB_s Ag.

Chronic HB_s Antigenaemia :

73 HB_s Ag positive patients were followed up for more than 6 months. Chronic antigenaemia (>6 months) occurred in 16 patients (21.9 %). The distribution of those cases among schistosomal and non-schistosomal patients is as follows .

	Non-schistosomal	Schistosomal
HB_s Ag +	40	33
Chronic antigenaemia	7 (17.5 %)	9 (27.3 %)
Mean minimal duration of antigenaemia.	155 days	255 days

Thus the schistosomal patients showed a marked tendency to chronic antigenaemia as shown both by a bigger percentage and - even more significantly-by a longer daration of antigenaemia.

Group		Number		Recovered	Chronicity	Deaths	Corrected Deaths
Non-Schisto	Total	80	No.	55	22	3	
			(%)	(68.75)	(27.5)	(3.75)	(2.6)
Schisto	Total	65	No.	26	37	2	
			(%)	(40)	(56.9)	(3.1)	(2.17)
Non-Schisto	Sex	Male:38	No.	24	14	0	
			(%)	(63.16)	(36.84)	0	
		Female:42	No.	31	8	3	
			(%)	(73.8)	(19.1)	(7.1)	(5.1)
Schisto	Sex	Male:62	No.	24	36	2	
			(%)	(38.4)	(58.1)	(3.2)	(2.4)
		Female:3	No.	2	1	0	
			(%)	(66.6)	(33.3)	0	
Non-Schisto	HB_S AG	+ 40	No.	25	13	2	
			(%)	(62.5)	(32.5)	(5)	(3.45)
		- 40	No.	30	9	1	
			(%)	(75)	(22.5)	(2.5)	(1.7)
Schisto	HB_S AG	+ 33	No.	11	20	2	
			(%)	(33.3)	(60.6)	(6.1)	(4.4)
		- 32	No.	15	17	0	
			(%)	(46.9)	(53.1)	0	

Table 6 : Outcome and sequelae of 145 patients with viral hepatitis.

Non Schisto = Non-Schistosomal group.

Schisto = Schistosomal group.

* This column contains the percent deaths related to the initial number of patients, within each group.

Comments

The course of the study shows some defects which need to be corrected during the subsequent period. The most important is to try to homogenize the patient groups as far as possible, particularly an increase in the schistosomal females. It is known however that the prevalence of schistosomiasis in this particular group is low due to exposure factors. Encouraging the follow-up is another important problem. The rate of performing liver biopsy is satisfactory but we shall try by all means to increase the number of patients rebiopsied after 1 year. Those should include schistosomal and non schistosomal patients.

Within the above limitations, the following preliminary deductions can be made.

a) Deaths are positively related to HB_s Ag, pregnancy and lactation.

b) Chronicity is unexpectedly high in the whole studied cases, evidenctly more in males, in HB_s Ag + cases and in schistosomal patients.

c) Chronic HB_s antigenaemia is more prevalent in schistosomal cases. We consider this an interesting finding which should be persued further, the following lines are planed :

- Relatinship to activity of schistosomal infection i.e.

living or dead ova.

- Effect of specific anti-schistosomal therapy.

These 2 approaches will point to a possible association of the hepatitis virus with the living parasite.

- Relationship to the humoral and cell-mediated aspects of the immune responses of the patients. A limiting factor here will be availability of specific antisera (anti-immunoglobulins) and reagents for skin testing for delayed hypersensitivity.

- Relationship to the histopathological feature as continuing portal inflammation or hepatocellular necrosis.

- Relationship to continuing evidence of functional disturbance of the liver.

d) The relevance of the viruses isolated from some patients will be examined for.